21. Taggart DP, Choudhary B, Anastasiadis K, Abu-Omar Y, Balacumaraswani L, Pigott DW. Preliminary experience with a novel intraoperative fluorescence imaging technique to evaluate the patency of bypass grafts in total arterial revascularization. Ann Thorac Surg 2003;75:870-3.
22. Reuthebuch O, Häussler A, Genoni M, Tavakoli R, Odavic D, Kadner A, et al. Novadaq SPY: intraoperative quality assessment in off-pump coronary artery bypass grafting. Chest 2004;125:418-24.
23. Balacumaraswani L, Abu-Omar Y, Choudhary B, Pigott D, Taggart DP. A comparison of transit-time flowmetry and intraoperative fluorescence imaging for assessing coronary artery bypass graft patency. J Thorac Cardiovasc Surg 2005;130:315-20.
24. Mitsuhashi N, Kimura F, Shimizu H, Imamaki M, Yoshidome H, Ohtsuka M, et al. Usefulness of intraoperative fluorescence imaging to evaluate local anatomy in hepatobiliary surgery. J Hepatobiliary Pancreat Surg 2008; 15:508-14.
25. Landsman ML, Kwant G, Mook GA, Zijlstra WG. Light-absorbing properties, stability, and spectal stabilization of indocyanine green. J Appl Physiol 1976;40:575-83.
26. Mordon S, Devoisselle JM, Soulie-Begu S, Desmettre T. Indocyanine green: physicochemical factors affecting its fluorescence in vivo. Microvasc Res 1998;55:146-52.
27. Mulllock BM, Shaw LJ, Fitzharris B, Peppard J, Hamilton MJ, Simpson MT, et al. Sources of proteins in human bile. Gut 1985;26:500-9.
28. Ishizawa T, Tamura S, Masuda K, Aoki T, Hasegawa K, Imamura H, et al. Intraoperative fluorescent cholangiography using indocyanine green: a biliary road map for safe surgery. J Am Coll Surg 2009;208:e1-4.
29. Strasberg SM, Belghiti J, Clavien P-A, et al. Terminology Committee of the International Hepato-Pancreato-Biliary Association. The Brisbane 2000 Terminology of Liver Anatomy and Resections. HPB 2000;2:333-9.
30. Couinaud C, editor. Le foie: etudes anatomiques et chirurgicales. Paris: Masson; 1957.
31. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
32. Neuhaus P. Complications of liver surgery and their management. In: Lygidakis NJ, Tytgat GNJ, editors. Hepatobiliary and pancreatic malignancies: diagnosis, medical and surgical management. New York: Thieme- Stratton Inc; 1989. p. 254-9.
33. Kohno H, Nagasue N, Chang YC, Taniura H, Yamanoi A, Nakamura T. Comparison of topical hemostatic agents in elective hepatic resection: a clinical prospective randomized trial. World J Surg 1992;16:966-9.
34. Li SQ, Liang LJ, Peng BG, Lu MD, Lai JM, Li DM. Bile leakage after hepatectomy for hepatolithiasis: risk factors and management. Surgery 2007;141:340-5.
35. Cherrick GR, Stein SW, Leevy CM, Davidson CS. Indocyanine green: observations on its physical properties, plasma decay, and hepatic extraction. J Clin Invest 1960;39:592-600.

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HEPATOLOGY

Evaluation of metabolic factors on the prognosis of patients undergoing resection of hepatocellular carcinoma

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angiotensin II blockade, hepatitis C virus, hepatectomy, hypertension, liver cancer.

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Abstract

Background and Aim: The metabolic factors including obesity, diabetes, and hypertension have been implicated as risk factors of hepatocellular carcinoma (HCC) in patients with chronic hepatitis. The effects of metabolic factors were investigated on the prognosis of patients undergoing resection of HCC.

Methods: A total of 469 HCC patients were classified into three groups; hepatitis B virus (HBV)-, hepatitis C virus (HCV)-, and non-HBV/HCV (NBC)-related HCC. Further, the patients with HCV-related HCC were sub-classified into three groups; the patients who did not have documented hypertension, hypertensive patients who received angiotensin II-blocking agents (ABA), and hypertensive patients who received no ABA.

Results: There were no significant difference of survival in the HBV-HCC and NBC-HCC patients with or without obesity, diabetes, and hypertension. In the patients with HCV-related HCC, however, hypertensive patients were significantly worse on both disease-free and overall survivals than non-hypertensive patients. Among the HCV-HCC patients with chronic hepatitis, hypertensive patients with ABA had significantly better preoperative liver function, and hypertensive patients without ABA were significantly worse on both disease-free and overall survivals than those of hypertensive patients with ABA and non-hypertensive patients.

Conclusions: Results suggest that hypertension is a risk factor for a poor prognosis after resection of HCV-related HCC. Angiotensin II blockade may improve the prognosis of hypertensive patients with early hepatic fibrosis after resection in HCV-related HCC.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide.[1] Although the majority of HCC patients are still found in Asia and Africa, recent studies have shown that the incidence and mortality rate of HCC are also rising in North America and Europe.[2,3] It has been estimated that the combined effect of hepatitis B and C viral infection accounts for more than 80% of HCCs worldwide.[4] In Japan, the Western lifestyle has become common in recent years, and the morbidity rates of obesity, diabetes, dyslipidemia, and hypertension have gradually increased. Metabolic syndrome is characterized by insulin resistance and is associated with atherosclerosis and hypertension, as well as being recognized as an inflammatory disease.[5,6] Obesity and diabetes have been shown to be associated with an increased risk of HCC in several epidemiological studies.[7–11] Recent studies have also indicated that diabetes is a risk factor for the progression of liver fibrosis and the development of HCC in patients with chronic hepatitis C.[12,13] These reports suggest that diabetes may contribute to a high postoperative recurrence rate of HCC. However, it remains controversial whether or not diabetes is an independent risk factor for the recurrence of HCC. Ikeda *et al.*[14] reported that diabetes was a risk factor for recurrent HCC after surgical treatment, while Poon *et al.*[15] and Toyota *et al.*[16] found that this was not so.

So far, little attention has been paid to the effect of hypertension on the long-term outcome after resection of HCC. Recent studies have shown that the renin-angiotensin system (RAS) plays a pivotal role in liver fibrosis.[17] The hepatic RAS is activated in chronic liver damage, and angiotensin II (AT-II) reportedly stimulates the contraction and proliferation of activated hepatic stellate cells (Ac-HSC) to increase transforming growth factor-β (TGF-β) expression via the angiotensin type-1 receptor (AT1-R). Some studies have demonstrated that the clinically available angiotensin-converting enzyme (ACE) inhibitors (ACE-I) and AT1-R blockers (ARB) can significantly improve both experimental and clinical liver fibrosis together with the suppression of Ac-HSC activation and TGF-β expression.[17]

In the present study, we classified HCC patients undergoing hepatectomy into groups with hepatitis B virus (HBV)-, hepatitis C virus (HCV)-, and non-HBV/HCV (NBC)-related HCC, and performed a detailed analysis of the impact of metabolic factors such as obesity, diabetes, and hypertension on the prognosis of

each group. In addition, to determine the influence of hypertension and antihypertensive therapy on the outcome of hepatectomy for HCV-HCC patients with chronic hepatitis or cirrhosis, we reviewed our experience of these two groups of patients.

Materials and methods

Subjects

Between February 1992 and December 2007, a total of 488 patients with HCC underwent R0 resection (defined as macroscopic removal of all tumors) at our institution. Nineteen patients died in hospital and the remaining 469 were followed up as outpatients. Serologic detection of any hepatitis antigen or antibody was considered to be evidence of hepatitis B virus (HBV) infection, while detection of hepatitis C antibody was considered to be evidence for hepatitis C virus (HCV) infection. Patients who were negative for both hepatitis B and C virus were classified as NBC. The metabolic factors investigated were obesity, diabetes, and hypertension. Obesity was assessed by calculating the body mass index (BMI; kg/m^2), and the subjects were categorized as normal (< 23 kg/m^2) or overweight (≥ 23 kg/m^2). When diagnosing diabetes according to the National Diabetes Data Group and American Diabetes Association diagnostic criteria,[18,19] the results of two common tests were used, which were the 75 g oral glucose tolerance test and fasting plasma glucose. Diabetes mellitus was treated with insulin or an oral hypoglycemic drug, or diet and/or exercise therapy for more than 3 years before surgery to control the blood glucose level. The definition of hypertension we used was that of the Seventh Joint National Committee on the Prevention, Detection, Evaluation and Treatment of Hypertension (VII JNC).[20] Hypertension was defined as documentation of a systolic blood pressure > 140 mmHg or a diastolic blood pressure > 90 mmHg on two occasions in the medical record. Hypertension was treated with one or more antihypertensive medication for more than 3 years before surgery. Patients who had hepatitis C infection were classified into groups with chronic hepatitis or cirrhosis by examination of resected liver tissue. The patients with chronic hepatitis C were also classified into the following three groups: Group I consisted of patients who did not have documented hypertension. Group II was hypertensive patients who had been treated with angiotensin II-blocking agents (ABA), which were defined as ACE-I (captopril, enalapril, alacepril, lisinopril, quinipril and trandolapril) or ARB (losartan, candesartan, valsartan and olmesartan). Group III was hypertensive patients who had been treated with other agents for their hypertension, including β-blockers, calcium channel antagonists, diuretics, α-blockers, and vasodilators.

Enteral nutrition for liver disease patients was provided as follows. Patients with chronic hepatitis or liver cirrhosis received a daily energy intake of 25–35 kcal/kgBW, a daily protein intake of 1.0–1.2 g/kgBW, and a daily sodium chloride intake of 5–7 g. In patients with diabetes or fatty liver, the daily energy intake was 20–25 kcal/kgBW. The daily sodium chloride intake was 6 g for hypertensive patients.

This study protocol was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Clinicopathologic variables and surgery

Before surgery, each patient underwent conventional liver function tests, measurement of the indocyanine green retention rate at 15 min (ICGR15), and technetium-99m-diethylenetriamine pentaacetic acid-galactosyl human serum albumin (^{99m}Tc-GSA) liver scintigraphy.[21] Hepatitis screening was done by measurement of hepatitis B surface antigen and hepatitis C antibody. The levels of α-fetoprotein (AFP) and protein induced by vitamin K absence/antagonism-II (PIVKA-II) were also measured in all patients. Surgical procedures were classified according to the Brisbane terminology proposed by Strasberg *et al.*[22] Anatomic resection was defined as resection of the tumor together with the related portal vein branches and the corresponding hepatic territory, and was classified as hemihepatectomy (resection of half of the liver), extended hemihepatectomy (hemihepatectomy plus removal of additional contiguous segments), sectionectomy (resection of two Couinaud subsegments[23]), or segmentectomy (resection of one Couinaud subsegment). All of the non-anatomic procedures were classified as limited resection. Tumors treated by limited resection consisted of both peripheral tumors and central tumors. Peripheral tumors and those with extrahepatic growth were treated by partial hepatectomy because this was able to achieve a sufficient surgical margin. Conversely, central tumors located near the hepatic hilum or major vessels were only treated by enucleation because it was too difficult/dangerous to remove enough tissue to obtain an adequate margin. One senior pathologist reviewed each specimen for histologic confirmation of the diagnosis. The width of the surgical margin was measured as the distance from the tumor edge to the line of resection.

Follow-up

Perioperative/postoperative complications and deaths were recorded to assess the morbidity and mortality of hepatectomy.

All of the patients who survived were followed up after discharge, with physical examination, liver function tests, ultrasound (US), computed tomography (CT), or magnetic resonance imaging (MRI) being performed at least every 3 months to check for intrahepatic recurrence, and chest radiographs being obtained to detect pulmonary metastasis. Chest CT was done if the chest radiograph showed abnormalities. Bone metastases were diagnosed by bone scintigraphy.

When recurrence of HCC was detected from changes of tumor markers or imaging findings, recurrence limited to the remnant liver was treated by transarterial chemoembolization (TACE), lipiodolization, re-resection, or percutaneous local ablative therapy such as radiofrequency ablation. After the detection of extrahepatic metastatses, active treatment was performed in patients with a good hepatic functional reserve (Child-Pugh class A or B) and good performance status (0 or 1), while other patients were only given radiation therapy for bone metastases to relieve symptoms. Surgical resection was done in patients with a solitary extrahepatic metastasis and no intrahepatic recurrence.

Prognostic factors

We performed univariate and multivariate analysis of 30 clinicopathologic factors to identify independent variables related to the

postoperative disease-free survival and overall survival of HCV patients classified into chronic hepatitis or cirrhosis groups based on examination of the resected liver. The patient factors studied were gender, age, alcohol abuse, liver function (including albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), prothrombin time, cholinesterase, platelet count, alkaline phosphatase (ALP), γ-glutamyltransferase (γGTP), ICGR15, GSA-Rmax, and Child-Pugh class), and the presence or absence of esophageal and/or gastric varices. The tumor factors studied were AFP, PIVKA-II, histologic features (including tumor diameter, differentiation, microscopic capsule formation, surgical margin, and microscopic vascular invasion), the number of tumors, and the tumor stage according to the Tumor Node Metastasis (TNM) classification.[24] The operative factors that we studied were the operating time, blood loss, perioperative blood transfusion, surgical procedure, and complications. All of the variables that were shown to be significant by univariate analysis were then examined with a Cox proportional hazards model to identify variables that had an independent influence on disease-free survival and overall survival.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation (SD). The significance of differences between two groups was assessed by the χ^2 test or the Mann–Whitney *U*-test, as was appropriate. The Kaplan–Meier method was used to calculate the disease-free survival rate and overall survival rate as of June 2008, and differences in survival were estimated with the generalized log-rank test. The Cox regression model (stepwise method) was used for multivariate analysis. In all analyses, $P < 0.05$ was considered to indicate statistical significance.

Results

Determinants of disease-free and overall survivals on univariate analysis

The disease-free survival rate and overall survival rate of the three viral groups stratified according to metabolic factors are compared in Table 1. There were no significant differences of disease-free survival or overall survival between the HBV-HCC and NBC-HCC patients with a BMI < 23 kg/m^2 or ≥ 23 kg/m^2, as well as between those with or without diabetes and those with or without hypertension. There were also no significant difference of disease-free survival and overall survival between the HCV-HCC patients with a BMI < 23 kg/m^2 or ≥ 23 kg/m^2 and between those with or without diabetes.

However, the 5-year disease-free survival rate and overall survival rate of HCV-HCC patients with or without hypertension was 18.4% and 13.4% versus 62.4% and 50.0%, respectively. There was a significant difference of both disease-free survival ($P = 0.0281$) and overall survival ($P = 0.0396$) between these two groups.

Prognosis of HCV-HCC patients having chronic hepatitis with or without hypertension

A total of 185 HCV-HCC patients had chronic hepatitis on examination of the resected liver tissue. Among these 185 patients, 106 patients did not have documented hypertension (Group I), 37 hypertensive patients received ABA (Group II), and 42 hypertensive patients received other agents without ABA (Group III). Table 2 summarizes the preoperative characteristics of these three groups. The incidence of diabetes was significantly higher in Group II compared with Groups I and III. The HbA_{1c} level of Group I was significantly lower than those of Groups II and III. Patients in Group II had significantly better preoperative liver function (ICGR15, GSA-Rmax, platelet count, serum total bilirubin, prothrombin time, and cholinesterase). Table 3 summarizes the perioperative parameters and pathologic findings of the three groups. The operating time, blood loss, blood transfusion, surgical procedure, and complications did not differ significantly among the three groups. Pathologic findings for the three groups are also listed in Table 3. No differences were detected with respect to tumor size, histology, microscopic capsular formation, a

Table 1 Univariate analysis of factors influencing disease-free survival and overall survival in patients with HBV-, HCV-, and NBC- HCC stratified by metabolic factors

Variable	No. patients	5-year disease-free survival (%)	*P*-value	5-year overall survival (%)	*P*-value
HBV					
Body mass index					
< 23 kg/m^2	38	33.0	0.8860	61.2	0.8509
≥ 23 kg/m^2	45	30.5		56.0	
Diabetes					
Absent	63	50.4	0.1421	63.1	0.2596
Present	20	39.0		55.8	
Hypertension					
Absent	62	35.7	0.3432	58.7	0.5828
Present	21	11.0		60.2	
HCV					
Body mass index					
< 23 kg/m^2	165	16.6	0.9658	59.7	0.2452
≥ 23 kg/m^2	161	16.2		54.9	
Diabetes					
Absent	251	17.1	0.7446	66.1	0.1445
Present	75	14.9		50.5	
Hypertension					
Absent	192	18.4	**0.0281**	62.4	**0.0396**
Present	134	13.4		50.0	
NBC					
Body mass index					
< 23 kg/m^2	20	37.4	0.3411	67.3	0.9579
≥ 23 kg/m^2	40	33.1		68.2	
Diabetes					
Absent	35	34.5	0.9463	75.3	0.2399
Present	25	33.7		63.6	
Hypertension					
Absent	36	36.5	0.8327	73.9	0.6045
Present	24	32.4		62.3	

HBV, hepatitis B virus; HCC, hepatocellular carcinoma (HCV), hepatitis C virus; NBC, non hepatitis B and C virus.

Table 2 Preoperative clinical characteristics of the three groups of HCV-HCC patients with chronic hepatitis

	Group I ($n = 106$)	Group II ($n = 37$)	Group III ($n = 42$)	*P*-value
Gender (male/female)	85/21	32/5	39/3	NS
Age (year)	65.4 ± 6.8	66.5 ± 7.6	67.1 ± 6.9	NS
BMI (kg/m^2)	21.8 ± 2.7	22.1 ± 3.0	22.5 ± 2.6	NS
Alcohol abuse (+/–)	50/56	20/17	21/21	NS
Other diseases				
Diabetes	12(11%)	14(38%)*[1]	6(14%)	*[1]$P = 0.0003$ and 0.0163 *vs.* I and III
Respiratory disease	6(6%)	0(0%)	1(2%)	NS
Renal disease	0(0%)	2(5%)	2(5%)	NS
HOMA-IR	1.79 ± 1.12	1.72 ± 1.28	2.21 ± 1.03	NS
HbA_{1c}	5.17 ± 0.85*[2]	6.07 ± 1.31	5.64 ± 1.21	*[2]$P = 0.0001$ and 0.0388 *vs.* II and III
Child-Pugh class A/B	96/10	36/1	41/1	NS
ICGR15 (%)	18.2 ± 8.7	14.7 ± 8.2*[3]	15.7 ± 9.0	*[3]$P = 0.0356$ *vs.* I
GSA Rmax (mg/min)	0.457 ± 0.189	0.588 ± 0.178*[4]	0.498 ± 0.200	*[4]$P = 0.0008$ and 0.0496 *vs.* I and III
Platelet count ($10^4/\mu L$)	13.9 ± 5.3	18.9 ± 8.8*[5]	15.2 ± 8.1	*[5]$P < 0.0001$ *vs.* I
Total bilirubin (mg/dL)	0.84 ± 0.30	0.67 ± 0.25*[6]	0.82 ± 0.38	*[6]$P = 0.0017$ and 0.0430 *vs.* I and III
Albumin (g/dL)	3.78 ± 0.38	3.79 ± 0.36	3.73 ± 0.44	NS
Prothrombin time (%)	87 ± 14	94 ± 12*[7]	89 ± 16	*[7]$P = 0.006$ *vs.* I
Cholinesterase (U/L)	107 ± 38	139 ± 62*[8]	113 ± 44	*[8]$P = 0.0003$ and 0.0347 *vs.* I and III
AST (U/L)	55 ± 40	51 ± 34	48 ± 27	NS
ALT (U/L)	60 ± 46	57 ± 41	49 ± 30	NS
ALP (U/L)	300 ± 157	310 ± 123	311 ± 102	NS
γ-GTP (U/L)	83 ± 100	78 ± 48	99 ± 75	NS
AFP (ng/mL)	716 ± 4438	322 ± 1056	203 ± 510	NS
PIVKA-II (mAU/mL)	2010 ± 7477	1016 ± 5518	4550 ± 12 294	NS
Esophageal and/or gastric varices (+/–)	19/87	5/32	6/36	NS

*[1–8]$P < 0.05$ was considered to indicate statistical significance.

Data represent the mean ± standard deviation or the number of patients.

Group I: non-hypertensive patients, Group II: hypertensive patients with ABA (ACE-I or ARBs), Group III: hypertensive patients without ABA (other antihypertensive agents).

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; γ-GTP, g-glutamyltransferase; GSA Rmax, maximum removal rate of technetium-99m-diethylenetriamine pentaacetic acid-galactosyl human serum albumin; HOMA-IR homeostasis model assessment insulin resistance index; ICGR15, indocyanine green retention rate at 15 min; PIVKA-II, protein-induced by vitamin K antagonism-II.

Table 3 Intraoperative and postoperative characteristics of the three groups of HCV-HCC patients with chronic hepatitis

	Group I ($n = 106$)	Group II ($n = 37$)	Group III ($n = 42$)	*P* value
Operating time (min)	276 ± 97	280 ± 103	307 ± 139	NS
Operative blood loss (ml)	1261 ± 1138	1011 ± 727	1465 ± 820	NS
Blood transfusion (+/–)	42/64	12/25	15/27	NS
Operative procedure (limited/anatomic resection)	86/20	28/9	32/10	NS
No. patients with complications	17(16%)	5(14%)	13(31%)	NS
Tumor size (cm)	3.81 ± 2.71	3.65 ± 2.54	3.89 ± 3.61	NS
Histology (well/moderately/poorly)	12/76/8	4/28/2	3/33/3	NS
fc (+/–)	96/10	34/3	38/4	NS
TW (+/–)	6/100	4/33	4/38	NS
vp and vv (+/–)	42/64	21/16	22/20	NS
Number of tumors (single/multiple)	86/20	29/8	29/13	NS
Tumor stage (I or II/III or IV)	79/27	23/14	26/16	NS

Data represent the mean ± standard deviation or the number of patients.

Group I: non-hypertensive patients, Group II: hypertensive patients with ABA (ACE-I or ARBs), Group III: hypertensive patients without ABA (other antihypertensive agents).

fc, microscopic capsular formation; HCV-HCC, hepatitis C virus hepatocellular carcinoma; NS, not significant; TW, microscopic margin < 5 mm from the tumor edge; vp, microscopic invasion of the portal vein; vv, microscopic invasion of the hepatic vein.

Table 4 Prognostic factors for disease-free survival and overall survival of patients with chronic hepatitis on multivariate analysis

(A) Disease-free survival

Variable	Coefficient	SE	Relative risk	*P*-value
Hypertension/ABA(-)	0.724	0.225	2.062	0.0013
Albumin < 3.8 g/dL	0.554	0.197	1.740	0.0049
ALP ≥ 285 U/L	0.580	0.197	1.786	0.0033
Multiple tumors	0.820	0.231	2.268	0.0004

(B) Overall survival

Variable	Coefficient	SE	Relative risk	*P*-value
Hypertension/ABA(-)	1.018	0.263	2.770	0.0001
Albumin < 3.8 g/dL	0.540	0.255	1.716	0.0344
Multiple tumors	0.985	0.265	2.681	0.0002

ABA, angiotensin II-blocking agents; ALP, alkaline phosphatase; SE, standard error.

microscopic surgical margin of < 5 mm, microscopic vascular invasion, number of tumors, and TNM stage.

Next, factors that had an influence on disease-free survival and overall survival in these patients were analyzed. Table 4 shows the results of multivariate analysis investigating the factors with an influence on disease-free survival and overall survival. Hypertension treated with antihypertensive agents other than ABA, albumin < 3.8 g/dL, ALP ≥ 285 U/L, and multiple tumors were selected as independent prognostic factors for disease-free survival, while hypertension treated with other antihypertensive agents, albumin < 3.8 g/dL, and multiple tumors were selected as factors that influenced overall survival.

The disease-free survival rate and overall survival rate of the three groups in HCV-HCC patients with chronic hepatitis are compared in Figure 1. The disease-free survival rate of Group III was significantly worse than that of Group I or II (Fig. 1a), with the respective rates being 14.7%, 49.3%, and 31.9% at 3 years, as well as 9.2%, 25.8%, and 8.9% at 5 years ($P < 0.0001$ and $P = 0.0033$, respectively). The overall survival rate of Group III was also significantly worse than that of Group I or II (Fig. 1b), with the respective rates being 58.3%, 79.6%, and 96.6% at 3 years, as well as 27.2%, 71.3%, and 80.5% at 5 years, and 17.0%, 60.1%, and 52.8% at 7 years ($P < 0.0001$ and $P = 0.0002$, respectively).

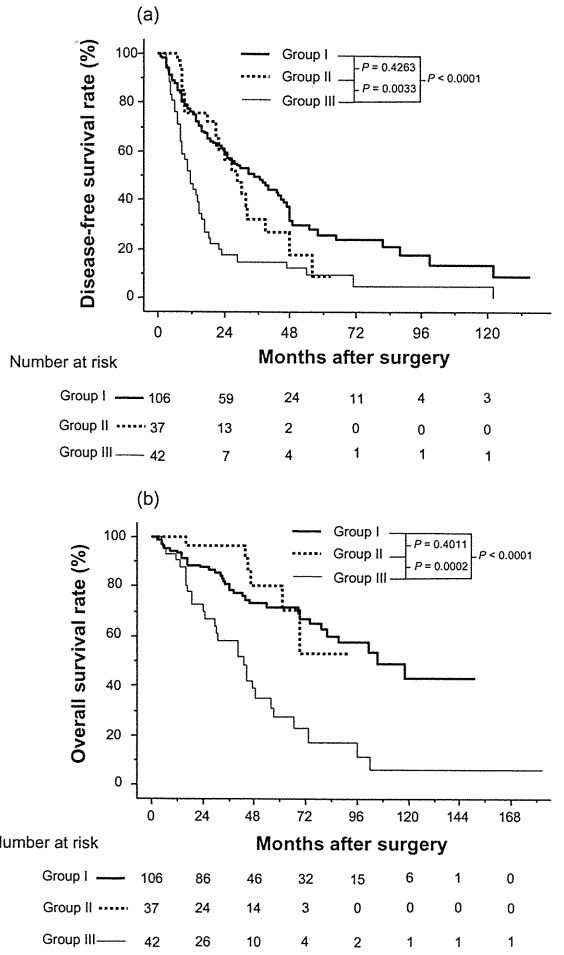

Figure 1 (a) Comparison of disease-free survival after resection of hepatocellular carcinoma (HCC) in three groups of hepatitis C virus (HCV) patients with chronic hepatitis. The disease-free survival rate of Group III (unbroken thin line) was significantly worse than that of Group I (unbroken thick line) and Group II (dotted line) ($P < 0.0001$ and $P = 0.0033$, respectively). (b) Comparison of overall survival after resection of HCC in three groups of HCV patients with chronic hepatitis. The overall survival rate of Group III (unbroken thin line) was significantly worse than that of Group I (unbroken thick line) and Group II (dotted line) ($P < 0.0001$ and $P = 0.0002$, respectively). The number of patients at risk is shown below the graph. (a) Group I; Group II; Group III; (b) Group I; Group II; Group III.

Prognosis of HCV-HCC patients having cirrhosis with or without hypertension

There were 141 HCV-HCC patients who had cirrhosis on examination of the resected liver tissue. Among these 141 patients, 86 patients did not have documented hypertension, 20 hypertensive patients received ABA, and 35 hypertensive patients received other antihypertensive agents without ABA. The preoperative, intraoperative, and postoperative clinical characteristics of these three groups were not significantly different.

Factors affecting the disease-free survival and overall survival of these HCV-HCC patients who had cirrhosis were also analyzed. Table 5 shows the results of multivariate analysis with the Cox proportional hazards model investigating factors with an influence on disease-free survival or overall survival. An age ≥ 68 years, tumor size ≥ 3.0 cm, multiple tumors, and poorly differentiated HCC were selected as independent prognostic factors for disease-free survival, while PIVKA ≥ 38 mAU/mL, esophageal and gastric varices, tumor size ≥ 3.0 cm, and multiple tumors were selected as factors with an influence on overall survival.

The disease-free survival rate and overall survival rate of the three groups in HCV-HCC patients with cirrhosis are compared in

Table 5 Prognostic factors for disease-free survival and overall survival of patients with cirrhosis on multivariate analysis

(A) Disease-free survival

Variable	Coefficient	SE	Relative risk	*P*-value
Age ≥ 68 years	0.606	0.222	1.835	0.0063
Tumor size ≥ 3.0 cm	0.627	0.216	1.873	0.0036
Multiple tumors	1.087	0.228	2.967	< 0.0001
Poor differentiation	0.955	0.345	2.597	0.0056

(B) Overall survival

Variable	Coefficient	SE	Relative risk	*P*-value
PIVKA-II ≥ 38 mAU/mL	0.651	0.276	1.916	0.0185
Esophageal and/or gastric varices	1.230	0.267	3.425	< 0.0001
Tumor size ≥ 3.0 cm	0.550	0.275	1.733	0.0485
Multiple tumors	0.802	0.257	2.232	0.0018

PIVKA-II, protein-induced by vitamin K antagonism-II; SE, standard error.

Figure 2. The disease-free survival rate of Groups I, II, and III was, respectively, 24.4%, 33.7%, and 21.8% at 3 years, as well as 8.8%, 22.5%, and 11.6% at 5 years. The overall survival rate of Groups I, II, and III was, respectively, 68.8%, 76.7%, and 55.4% at 3 years; 51.6%, 76.7%, and 37.3% at 5 years; and 31.7%, 59.7%, and 31.1% at 7 years. There were no significant differences of disease-free survival among the three groups, but the overall survival rate of Group III was significantly worse than that of Group II ($P = 0.0295$).

Discussion

In Japan, the Western lifestyle has recently become common, leading to higher rates of obesity, diabetes, dyslipidemia, and hypertension. Because hepatitis (B or C) is a major risk factor for HCC, it is important to determine whether metabolic disease has a different influence on the prognosis of HCC, depending on whether patients have HBV-, HCV-, or NBC-related cancer. In the present study therefore, patients with HBV-, HCV-, and NBC-related HCC were examined to determine the impact of metabolic factors on the prognosis of HCC after surgical resection.

In the present study, there were no significant differences of disease-free survival and overall survival between HBV-HCC, HCV-HCC, and NBC-HCC patients with or without diabetes, and a higher preoperative BMI was not associated with the outcome of surgical treatment in the HBV-HCC, HCV-HCC, and NBC-HCC groups (Table 1). In contrast, among HCV-HCC patients, both disease-free survival and overall survival after resection were worse in the patients with hypertension than in those without hypertension (Table 1). Compared with HBV-HCC patients, HCV patients were older and had more morbidity related to hypertension.[25] HCV-HCC patients also had more severe cirrhosis compared with HBC-HCC patients.[26] The prognosis of HCV-HCC is worse than that of HBV-HCC,[26] because multicentric carcinogenesis is more common in patients with HCV infection than in

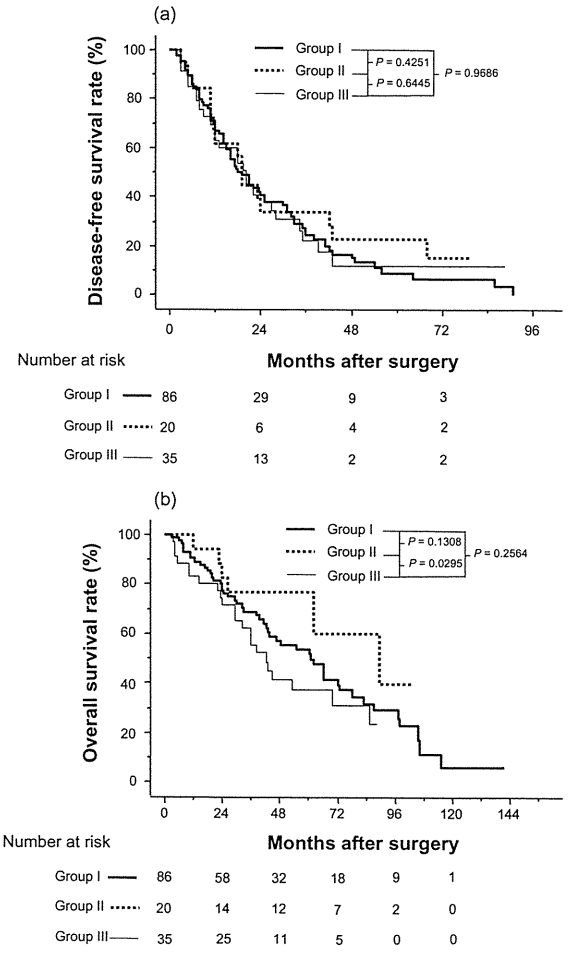

Figure 2 (a) Comparison of disease-free survival after resection of hepatocellular carcinoma (HCC) in three groups of hepatitis C virus (HCV) patients with cirrhosis. There was no significant difference of disease-free survival among the three groups. (b) Comparison of overall survival after resection of HCC in three groups of HCV patients with cirrhosis. The overall survival rate of Group III (unbroken thin line) was significantly worse than that of Group II (dotted line) ($P = 0.0295$). The number of patients at risk is shown below the graph. (a) Group I; Group II; Group III; (b) Group I; Group II; Group III.

patients with HBV infection.[27–29] However, the reason for the survival difference between HBV and HCV patients with hypertension remains unclear.

Grossman *et al.* performed a meta-analysis and reported that hypertension was associated with a 23% increase in the risk of cancer death.[30] A variety of angiogenic and other growth factors are increased in persons with hypertension and may also be involved in carcinogenesis.[31,32] Our results suggest that hypertension may worsen the prognosis after resection of HCC, because hepatocarcinogenesis and neovascularization are promoted by various circulating factors that are increased in hypertension.

In HCV-HCC patients with chronic hepatitis, hypertensive patients receiving ABA had significantly better preoperative liver function than those without ABA (Table 2). Hypertension treated with antihypertensive agents other than ABA was found to be an independent prognostic factor for both disease-free survival and overall survival by multivariate analysis (Table 4). Finally, the disease-free survival and overall survival of hypertensive HCV-HCC patients receiving ABA, as well as non-hypertensive patients, were significantly better than those of hypertensive patients treated with other antihypertensive agents (Fig. 1). These results demonstrated that AT-II blockade by ACE-I or ARB markedly improved the prognosis of HCC after hepatectomy in HCV patients with hypertension. It has already been reported that ACE-I or ARB markedly improved the liver fibrosis score and TGF-β expression in patients with chronic hepatitis C and non-alcoholic steatohepatitis.[17] In addition, Corey *et al.*[33] reported that hypertensive HCV-patients receiving ABA had less fibrosis than hypertensive patients without ABA therapy. They suggested an association with hypertension, possibly via the RAS, in the development of fibrosis, and a beneficial effect of AT-II blockade on HCV-related fibrosis.

However, there was no significant difference of disease-free survival between HCV-HCC patients who had cirrhosis with or without hypertension (Fig. 2a). Factors that influenced the disease-free survival and overall survival of HCV-HCC patients with cirrhosis according to multivariate analysis were tumor-related factors, including tumor size and the presence of multiple tumors. Therefore, in HCV-HCC patients with cirrhosis, survival depended on the progression of the tumor itself and was not related to the existence of hypertension. ABA therapy is not likely to prevent tumor recurrence in the cirrhotic liver.

In conclusion, hypertension appears to increase the risk of a poor prognosis after resection of HCV-related HCC. However, hypertensive HCV-HCC patients receiving ACE-I or ARB therapy had significantly better preoperative liver function and angiotensin II blockade by ABA improved the prognosis after hepatectomy in hypertensive HCV-HCC patients with early liver fibrosis. These findings should be taken into consideration when treating HCC. Further prospective studies will be required to fully evaluate the effect of inhibiting angiotensin II by ACE-I and ARB in hypertensive patients with potentially curable HCC.

References

1 Bosch X, Ribes J, Borras J. Epidemiology of primary liver cancer. *Semin. Liver Dis.* 1999; **19**: 271–85.
2 Taylor-Robinson SD, Foster GR, Arora S *et al.* Increase in primary liver cancer in the UK 1979–94. *Lancet* 1997; **350**: 1142–3.
3 El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N. Engl. J. Med.* 1999; **340**: 745–50.
4 Bosch FX, Ribes J, Diaz M *et al.* Primary liver cancer: worldwide incidence and trends. *Gastroenterology* 2004; **127**: S5–S16.
5 Ferrannini E, Buzzigoli G, Bonadonna R *et al.* Insulin resistance in essential hypertension. *N. Engl. J. Med.* 1987; **317**: 350–7.
6 Ross R. Atherosclerosis: an inflammatory disease. *N. Engl. J. Med.* 1999; **340**: 115–26.
7 Moller H, Mellemgaard A, Lindvig K *et al.* Obesity and cancer risk: a Danish record-linkage study. *Eur. J. Cancer* 1994; **30A**: 344–50.
8 Rapp K, Schroeder J, Klenk J *et al.* Obesity and incidence of cancer: a large cohort study of over 145 000 adults in Austria. *Br. J. Cancer* 2005; **93**: 1062–7.
9 Calle EE, Rodriguez C, Walker-Thurmond K *et al.* Overweight, obesity and mortality from cancer in a prospective studied cohort of US adults. *N. Engl. J. Med.* 2003; **348**: 1625–38.
10 Samanic C, Gridley G, Chow WH *et al.* Obesity and cancer risk among white and black United States veterans. *Cancer Causes Control* 2004; **15**: 35–43.
11 Nair S, Mason A, Eason J *et al.* Is obesity an independent risk factor for hepatocellular carcinoma in cirrhosis? *Hepatology* 2002; **36**: 150–5.
12 El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 2004; **126**: 460–8.
13 Davila JA, Morgan RO, Shaib Y *et al.* Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. *Gut* 2005; **54**: 533–9.
14 Ikeda Y, Shimada M, Hasegawa H *et al.* Prognosis of hepatocellular carcinoma with diabetes mellitus after hepatic resection. *Hepatology* 1998; **27**: 1567–71.
15 Poon RT, Fan ST, Wong J. Dose diabetes mellitus influence the perioperative outcome or long term prognosis after resection of hepatocellular carcinoma. *Am. J. Gastroenterol.* 2002; **97**: 1480–8.
16 Toyoda H, Kumada T, Nakano S *et al.* Impact of diabetes mellitus on the prognosis of patients with hepatocellular carcinoma. *Cancer* 2001; **91**: 957–63.
17 Yoshiji H, Kuriyama S, Fukui H. Blockade of renin-angiotensin system in antifibrotic therapy. *J. Gastroenterol. Hepatol.* 2007; **22**: S93–S95.
18 National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 1979; **28**: 1039–57.
19 American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2008; **31** (Suppl 1): S55–60.
20 Chobanian AV, Bakris GL, Black HR *et al.* The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–72.
21 Kwon AH, Ha-Kawa SK, Uetsuji S *et al.* Preoperative determination of the surgical procedure for hepatectomy using technetium-99m-galactosyl human serum albumin (99mTc-GSA) liver scintigraphy. *Hepatology* 1997; **25**: 426–9.
22 Strasberg SM, Belghiti J, Clavn P-A *et al.* The Brisbane 2000 terminology of liver anatomy and resection. Terminology Committee of the International Hepato-Pancreato-Biliary Association. *HPB* 2000; **2**: 333–9.
23 Couinaud C, ed. *Le Foie: Etudes Anatomiques Et Chirurgicales.* Paris: Masson, 1957.
24 Sobin LH, Wittekind C, eds. *TNM Classification of Malignant Tumours*, 5th edn. New York: Wiley, 1997.
25 Chen CL, Yang H, Yang WS *et al.* Metabolic factors and risk of hepatocellular carcinoma by chronic hepatitis B/C infection: a follow-up study in Taiwan. *Gastroenterology* 2008; **135**: 111–21.
26 Shiratori Y, Shiina S, Imamura M *et al.* Characteristic difference of hepatocellular carcinoma between hepatitis B- and C- viral infection in Japan. *Hepatology* 1995; **22**: 1027–33.
27 Miyagawa S, Kawasaki S, Makuuchi M. Comparison of the characteristics of hepatocellular carcinoma between hepatitis B and C viral infection: tumor multicentricity in cirrhotic liver with hepatitis C. *Hepatology* 1996; **24**: 307–10.

28 Kubo S, Nishiguchi S, Hirohashi K *et al.* Clinicopathological criteria for multicentricity of hepatocellular carcinoma and risk factors for such carcinogenesis. *Jpn. J. Cancer Res.* 1998; **89**: 419–26.
29 Shuto T, Hirohashi K, Kubo S *et al.* Differences of resected hepatocellular carcinoma with hepatitis B or C virus. *Hepatogastroenterology* 1998; **45**: 1722–5.
30 Grossman E, Messerli FH, Boyko V *et al.* Is there an association between hypertension and cancer mortality? *Am. J. Med.* 2002; **112**: 479–86.
31 Chow WH, Gridley G, Fraumeni JF *et al.* Obesity, hypertension, and the risk of kidney cancer in men. *N. Engl. J. Med.* 2000; **343**: 1305–11.
32 Yoshiji H, Noguchi R, Ikenaka Y *et al.* Renin-angiotensin system inhibitors as therapeutic alternatives in the treatment of chronic liver diseases. *Curr. Med. Chem.* 2007; **14**: 2749–54.
33 Corey KE, Shah N, Misdraji J *et al.* The effect of angiotensin-blocking agents on liver fibrosis in patients with hepatitis C. *Liver International.* 2009; **29**: 748–53.

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ORIGINAL ARTICLE

Predictors and outcome of early recurrence after resection of hepatic metastases from colorectal cancer

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Abstract
Purpose This study aimed to investigate the risk factors for early recurrence in patients who had undergone curative resection of colorectal liver metastases (CRLM) and to evaluate the outcome after recurrence.
Methods A total of 119 patients were divided into 2 groups: an early recurrence group (n=54) who had recurrence within 2 years of curative resection of CRLM and a 2-year recurrence-free group (n=65) who remained disease-free for at least 2 years following surgery.
Results During the initial 5-year period after surgery, 4 out of 65 patients (6%) in the 2-year recurrence-free group and 29 out of 54 patients (54%) in the early recurrence group died. Multivariate analysis showed that postoperative morbidity was an independent predictor of early recurrence after curative resection of CRLM.
Conclusions Early recurrence is the leading cause of death within 5 years after curative resection of CRLM. Postoperative morbidity increases the risk of early recurrence in these patients. A reduction in perioperative morbidity may, therefore, improve the outcome of curative resection, as well as reducing medical costs.

Keywords Colorectal cancer liver metastases · Hepatic resection · Early recurrence · Risk factor

Synopsis for table of contents Early recurrence is the leading cause of death within 5 years after curative resection of liver metastases from colorectal cancer. Postoperative morbidity influences early recurrence in patients with colorectal liver metastases.

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Introduction

Hepatic resection is currently the only potentially curative treatment for colorectal liver metastases (CRLM). Results from various specialist hepatobiliary centers have shown that surgical resection can potentially achieve a 5-year survival rate of 20–46% [1–7]. However, recurrence is a major problem after surgery, since it occurs in 80–85% of patients [1, 8, 9]. Reducing the recurrence rate is, therefore, necessary to improve the prognosis after resection of CRLM. A shorter interval until recurrence after resection of the primary tumor is correlated with a poorer prognosis in patients with colorectal cancer [8, 10], breast cancer [11], hepatocellular carcinoma [12], and renal cell carcinoma [13]. However, the relationship between the time to recurrence after resection of CRLM and prognosis is still unclear. After complete resection of CRLM, early recurrence (defined as intrahepatic, regional, or systemic recurrence within 2 years) is reported to be one of the most important factors determining prognosis. Tumor characteristics that have been reported to show an association with early recurrence include a high level of carcinoembryonic antigen (CEA), multiple metastases, a positive surgical margin, and a high clinical risk score [1, 8, 10, 14–19], but the relative importance of each of these factors is unclear.

The present study aimed to identify risk factors for early recurrence following curative resection of CRLM and to evaluate the prognosis after recurrence.

Materials and methods

Patients

Between February 1993 and March 2007, a total of 119 patients with CRLM underwent curative resection at our institution. Curative resection was defined as macroscopic removal of all hepatic tumors. None of the patients died in the hospital, and follow-up data were available until death or for more than 2 years in all cases. This study was performed by retrospective review of the medical records. Based on their status at 2 years after resection, the subjects were divided into an early recurrence group (n=54) composed of patients who suffered recurrence within 2 years after surgery and a 2-year recurrence-free group (n=65) composed of patients with no evidence of recurrence after 2 years of follow-up.

Clinicopathologic variables and surgery

Before surgery, each patient underwent conventional liver function tests and measurement of the indocyanine green retention rate at 15 min (ICGR15). The levels of CEA and cancer antigen 19-9 (CA19-19) were also measured in all patients. Preoperative radiological assessment always included computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. Intraoperative ultrasound (US) was performed to confirm the preoperative imaging findings and to assist in planning the surgical procedure. According to the Brisbane terminology proposed by Strasberg et al. [20], anatomic resection was defined as resection of the tumor together with the related portal vein branches and the corresponding hepatic territory. Anatomic resection was classified as hemihepatectomy (resection of half of the liver), extended hemihepatectomy (hemihepatectomy plus removal of additional contiguous segments), sectionectomy (resection of two Couinaud subsegments [21]), or segmentectomy (resection of one Couinaud subsegment). All nonanatomic procedures were classified as limited resection, while anatomic plus limited resection was classified as combined resection. One senior pathologist reviewed each resected specimen for histologic confirmation of the diagnosis. The width of the surgical margin was measured as the distance from the tumor edge to the resection line. The clinical risk score [10] (possible range, 0 to 5 points) was calculated by assigning 1 point for each of the following: positive nodal status of the primary colorectal tumor, disease-free interval of <1 year from resection of the primary tumor to the detection of liver metastasis, preoperative CEA level >200 ng/ml, more than one liver tumor, and largest tumor >5 cm in diameter.

Follow-up

Postoperative complications were investigated to assess morbidity following hepatectomy and were classified according to the Clavien system [22]. Briefly, grade I is any deviation from the normal postoperative course not requiring special treatment. Grade II is an event requiring pharmacological treatment. Grade III is an event requiring surgical or radiological intervention, without (IIIa) or with (IIIb) general anesthesia. Grade IV is a life-threatening complication, involving single (IVa) or multiple (IVb) organ dysfunction. Grade V is death. After discharge from the hospital, patients were reviewed at least every 3 months to check for intrahepatic recurrence based on the results of physical examination, liver function tests, and abdominal US, CT, or MRI. Chest X-rays were undertaken every 3 months and chest CT scans were undertaken every 6 months to detect pulmonary metastases. In patients with bone pain, scintigraphy was undertaken to detect bone metastases.

If recurrence of liver metastases was detected by changes in tumor markers or by imaging, recurrence that was limited to the remnant liver was treated by repeat resection or by percutaneous local therapy such as radiofrequency ablation. If extrahepatic metastases were detected, active treatment was undertaken in patients with a good performance status (0 or 1). In patients with bone metastases, radiation therapy was undertaken to relieve symptoms. Surgical resection was undertaken in patients with a solitary extrahepatic metastasis and no evidence of intrahepatic recurrence.

Prognostic factors

We performed univariate and multivariate analyses of various clinicopathologic factors to identify independent variables that could predict early recurrence of CRLM. The patient factors studied were gender, age, body mass index (BMI), primary tumor site, primary tumor lymph node status, primary tumor histology, primary tumor stage, preoperative neoadjuvant chemotherapy, postoperative chemotherapy, timing of hepatic metastasis (synchronous or metachronous), and liver function (including albumin, prothrombin time, and ICGR15). The operative factors studied were blood loss, perioperative blood transfusion, surgical procedure, extent of liver resection, postoperative morbidity, postoperative hospital stay, and repeat resection.

The tumor factors studied were CEA, CA19-9, tumor size, number of metastases, distribution of metastases, extrahepatic nodal disease, surgical margin, coexisting liver disease, and clinical risk score. Variables that were shown to be significant by univariate analysis were re-examined using a univariate and multivariate logistic regression model to identify independent predictors of early recurrence after curative resection.

Statistical analysis

For continuous variables, subjects were categorized into two groups divided by the median values, and the significance of differences between each pair of groups was assessed by the chi-square test. Categorical data were compared with the chi-square test and Fisher's exact test where appropriate. Multivariate logistic regression analysis was performed by the backward elimination method using all variables. The variable with the highest p value for the estimated odds ratio was excluded if $p>0.2$, and this process was repeated until all p values were <0.2. By subsequently individually adding the excluded variables to the final model, it was confirmed that none of these variables had a p value <0.2.

The Kaplan–Meier method was employed to calculate the time to recurrence, median survival, recurrence-free survival, and overall survival as of March 2009, and differences in survival were assessed by the generalized log-rank test. In all analyses, $p<0.05$ was considered to indicate statistical significance.

Results

Preoperative characteristics

Table 1 summarizes the preoperative characteristics of the early recurrence and 2-year recurrence-free groups. No differences were detected between the two groups with respect to gender, age, BMI, primary tumor site, primary tumor lymph node status, primary tumor histology, primary tumor stage, timing of hepatic metastasis, CEA, CA19-9, or liver function. Neoadjuvant chemotherapy was administered to 20 patients (37%) for a median of 5 months (range, 1–22 months) in the early recurrence group and to 28 patients (43%) for a median of 7 months (range, 1–18 months) in the 2-year disease-free group. The neoadjuvant chemotherapy regimens administered before hepatectomy did not differ significantly between the two groups.

Perioperative parameters and pathologic findings

As shown in Table 2, the operative blood loss, blood transfusion rate, surgical procedures, and extent of liver resection did not differ significantly between the two groups.

Table 1 Preoperative clinical characteristics of the two groups

Variable	Early recurrence group (n=54)	2-year recurrence-free group (n=65)	p value
Gender (male/female)	32/22	38/27	0.9299
Age >64 years	28 (52%)	34 (52%)	0.9605
BMI >23 kg/m^2	27 (50%)	35 (54%)	0.6758
Primary tumor (colon/rectum)	38/16	48/17	0.6733
Primary tumor nodal status (negative/positive)	17/37	22/43	0.7844
Primary tumor histology (well or moderate/poor or mucinous)	51/3	56/9	0.1348
Primary tumor stage (T1 or T2/T3 or T4)	7/47	5/60	0.3418
Preoperative neoadjuvant chemotherapy (no/yes)	34/20	37/28	0.5037
5-FU/LV	10 (50%)	16 (57%)	0.8745
5-FU/LV with irinotecan (CPT-11)	7 (35%)	8 (29%)	
5-FU/LV with oxaliplatin	3 (15%)	4 (14%)	
Timing of hepatic metastasis (metachronous/synchronous)	17/37	28/37	0.1941
CEA >6 ng/ml	27 (50%)	25 (38%)	0.2065
CA19-9 >30 ng/dl[a]	19 (49%)	22 (41%)	0.4445
Albumin >4.0 mg/dl[a]	26 (49%)	33 (52%)	0.7213
Prothrombin time >100%[a]	28 (56%)	36 (57%)	0.9031
ICGR15 >9%[a]	25 (60%)	23 (48%)	0.2708

Data represent the number of patients

BMI body mass index, *5-FU* 5-fluorouracil, *LV* leucovorin, *CEA* carcinoembryonic antigen, *ICGR15* indocyanine green retention rate at 15 min

[a]Indicated data were not available for all patients

Table 2 Intraoperative and postoperative characteristics of the two groups

Variable	Early recurrence group (n=54)	2-year recurrence-free group (n=65)	p value
Operative blood loss >800 ml	29 (54%)	29 (45%)	0.3234
Blood transfusion	20 (37%)	25 (38%)	0.8732
Surgical procedure			0.2671
Anatomic resection	14 (26%)	23 (35%)	
Limited or combined resection	40 (74%)	42 (65%)	
Extent of liver resection			0.4712
Less than hemihepatectomy	34 (63%)	45 (69%)	
Hemihepatectomy or more	20 (37%)	20 (31%)	
Postoperative morbidity	20 (37%)	7 (11%)	0.0007
Bile leakage	5	3	
Intra-abdominal abscess	5	3	
Liver failure	5	0	
Pneumonia	2	0	
Colitis	1	1	
Pleural effusion	1	0	
Ileus	1	0	
Grade of surgical complications			0.6518
I	0	0	
II	0	0	
IIIa	9 (45%)	5 (71%)	
IIIb	4 (20%)	1 (14%)	
IVa	6 (30%)	1 (14%)	
IVb	1 (5%)	0	
V	0	0	
Postoperative hospital stay >20 days	34 (63%)	27 (42%)	0.0199
Postoperative chemotherapy (no/yes)	24/30	39/26	0.0905
5-FU/LV	6 (20%)	4 (15%)	0.7321
5-FU/LV with irinotecan (CPT-11)	3 (10%)	5 (19%)	
5-FU/LV with oxaliplatin	7 (23%)	7 (27%)	
Others	14 (47%)	10 (38%)	
Tumor size >3.5 cm	27 (50%)	32 (49%)	0.9334
No. of metastases ≥3	24(44%)	14 (22%)	0.0076
Distribution of metastases (unilobar/bilobar)	30/24	47/18	0.0569
Extrahepatic nodal disease	5 (9%)	4 (6%)	0.5236
Positive surgical margin	13 (24%)	9 (14%)	0.1525
Coexisting liver disease	11 (20%)	15 (23%)	0.7220
Repeat resection	9 (17%)	6 (9%)	0.2237
Clinical risk score >2	25 (46%)	19 (29%)	0.0549
Median time to recurrence (months)	10.0	30.0	<0.0001
Median survival (months)	21.5	38.0	<0.0001

Data represent the number of patients

However, patients in the early recurrence group had a higher perioperative morbidity rate and a longer postoperative hospital stay compared with those in the 2-year recurrence-free group. The grades of surgical complications according to the Clavien classification did not differ significantly between the two groups.

Postoperative chemotherapy was administered to 30 patients (56%) in the early recurrence group and to 26 patients (40%) in the 2-year disease-free group. The chemotherapy regimens administered after hepatectomy did not differ significantly between the two groups.

The pathologic findings obtained in the two groups are also listed in Table 2. Although the early recurrence group had a significantly higher number of metastases, the other pathologic characteristics did not differ significantly between the two groups.

Factors related to early recurrence

Variables in Table 3 with a p value <0.05 showed an association with early recurrence, and variables with p values ≥0.05 showed a possible association with recurrence. The other 21 variables were not associated with recurrence. Multivariate analysis showed that postoperative morbidity was the only independent predictor of early recurrence after curative resection of CRLM (odds ratio= 4.70; 95% CI=0.08 to 0.59; p=0.003) (Table 3).

Recurrence and survival

The median follow-up period was 31 months (range, 24–157 months). Early recurrence was detected as solitary or multifocal intrahepatic tumor in 38 patients and as metastasis to other sites in 16 patients (lung metastasis in 10, hepatoduodenal lymph node metastasis in 3, bone metastasis in 2, and intrahepatic plus lung metastasis in 1). In 36 of the 38 patients with intrahepatic recurrence, the new tumors arose further than 1 cm from the surgical margin, while the tumors were located at the margin in the remaining two patients. In the 2-year recurrence-free group, 10 out of 65 patients (15%) eventually developed recurrence after more than 2 years. Six of these patients had intrahepatic recurrence and four had lung metastases. Among all 119 patients with CRLM, 44 (37%) developed recurrence in the remnant liver. Late recurrence after resection was detected in 10 out of 119 (8%) of the patients in this series.

The disease-free survival rate and overall survival rate for all 119 patients were 38.7% and 67.8% at 3 years and 33.7% and 57.6% at 5 years, respectively. The median survival time and the time to recurrence after resection were 37 and 17 months, respectively. The median time to recurrence after resection in the 2-year recurrence-free group and early recurrence groups was 30.0 and 10.0 months, respectively (Table 2). The median survival time after resection in the 2-year recurrence-free and early recurrence groups was 38 and 21.5 months, respectively. Overall survival rates of the early recurrence and 2-year recurrence-free groups were 36.4% and 98.0% at 3 years, 24.2% and 87.8% at 5 years, and 18.2% and 87.8% at 7 years, respectively. There were significant differences in recurrence-free survival and overall survival between the early recurrence and 2-year recurrence-free groups (both p<0.0001). Of the 54 patients in the early recurrence group, 29 (54%) died within 5 years after curative resection. Of the 65 patients in the 2-year recurrence-free group, 4 (6%) died within 5 years of curative resection. All 33 deaths were directly attributable to metastatic colorectal cancer.

In the early recurrence group, 38 of the 54 patients (70%) underwent additional therapy after the detection of recurrence (9 underwent repeat resection of hepatic tumors, 1 received percutaneous microwave coagulation therapy, 1 received radiofrequency ablation, 6 received local chemotherapy via a reservoir, and 21 received systemic chemotherapy). In the 2-year recurrence-free group, 10 of the 65 patients (10%) eventually developed recurrence and underwent additional therapy (6 underwent repeat resection of hepatic tumors, 1 underwent resection of a solitary lung metastasis, and 3 received systemic chemotherapy).

Table 3 Multivariate analysis of factors predicting early recurrence after resection of liver metastases

Variable	Odds ratio	95% CI	p value
Poor clinical risk score	1.40	0.86–2.28	0.171
Bilobar metastases	1.94	0.78–4.80	0.152
Higher primary tumor stage	2.06	0.21–1.13	0.094
Postoperative morbidity	4.70	0.08–0.59	0.003

CI confidence interval

Perioperative characteristics and postoperative survival rates of patients with and without postoperative morbidity

Table 4 summarizes the perioperative characteristics of the patients with and without postoperative morbidity. No differences were detected between the two groups with respect to age, BMI, timing of hepatic metastasis, CEA, albumin, ICGR15, surgical procedure, extent of liver resection, tumor size, number of metastases, distribution of metastases, extrahepatic nodal disease, positive surgical margin, coexisting liver disease, repeat resection, or clinical risk score. Preoperative neoadjuvant chemotherapy was administered to 10 patients (37%) with morbidity and to 38 patients (41%) without morbidity. The neoadjuvant chemotherapy regimens administered before hepatectomy did not differ significantly between the two groups. Postoperative chemotherapy was administered to 10 patients (37%) with morbidity and to 46 patients (50%) without morbidity. The chemotherapy regimens administered after hepatectomy did not differ significantly between the two groups. Operative blood loss was greater among patients with postoperative morbidity than patients without, and the incidence of blood transfusion was also higher among patients with postoperative morbidity than patients without. Of the patients with postoperative morbidity, 20 out of 27 (74%) eventually developed recurrence.

The 5-year recurrence-free and overall survival rates among patients with postoperative morbidity were 17.5% and 42.4%, respectively, and among patients without morbidity were 38.8% and 63.4%, respectively (Fig. 1). There were significant differences in both recurrence-free survival (p=0.0009) and overall survival (p=0.001) between the groups with and without postoperative morbidity.

Table 4 Perioperative characteristics of the groups with and without postoperative morbidity

Variable	Morbidity (n=27)	No morbidity (n=92)	p value
Age >64 years	15 (56%)	47 (51%)	0.6828
BMI >23 kg/m^2	10 (37%)	52 (57%)	0.0747
Preoperative neoadjuvant chemotherapy (no/yes)	17/10	54/38	0.6911
5-FU/LV	7 (70%)	19 (50%)	0.2963
5-FU/LV with irinotecan (CPT-11)	3 (30%)	12 (32%)	
5-FU/LV with oxaliplatin	0 (0%)	7 (18%)	
Timing of hepatic metastasis (metachronous/synchronous)	8/19	37/55	0.3185
CEA >6 ng/ml	15 (56%)	37 (40%)	0.1577
Albumin >4.0 mg/dl[a]	9 (35%)	50 (56%)	0.0599
ICGR15 >9%[a]	10 (50%)	38 (54%)	0.7347
Operative blood loss >800 ml	19 (70%)	39 (42%)	0.0105
Blood transfusion	16 (59%)	29 (32%)	0.0090
Surgical procedure			
Anatomic resection	8 (30%)	29 (32%)	0.8518
Limited or combined resection	19 (70%)	63 (68%)	
Extent of liver resection			
Less than hemihepatectomy	21 (78%)	58 (63%)	0.1541
Hemihepatectomy or more	6 (22%)	34 (37%)	
Postoperative chemotherapy (no/yes)	17/10	46/46	0.2354
5-FU/LV	2 (20%)	8 (17%)	0.8252
5-FU/LV with irinotecan (CPT-11)	2 (20%)	6 (13%)	
5-FU/LV with oxaliplatin	3 (30%)	11 (24%)	
Others	3 (30%)	21 (46%)	
Tumor size >3.5 cm	16 (59%)	43 (47%)	0.2526
No. of metastases ≥3	10 (37%)	28 (30%)	0.5176
Distribution of metastases (unilobar/bilobar)	19/8	58/34	0.4836
Extrahepatic nodal disease	3 (11%)	6 (7%)	0.4278
Positive surgical margin	8 (30%)	14 (15%)	0.0898
Coexisting liver disease	4(15%)	22 (24%)	0.3144
Repeat resection	3 (11%)	12 (13%)	0.7902
Clinical risk score >2	14 (52%)	30 (33%)	0.0686
Recurrence within 2 years after surgery	20 (74%)	34 (37%)	0.0007

Data represent the number of patients

BMI body mass index, *5-FU* 5-fluorouracil, *LV* leucovorin, *CEA* carcinoembryonic antigen, *ICGR15* indocyanine green retention rate at 15 min

[a]Indicated data were not available for all patients

Discussion

Surgical resection offers the only possibility of cure for patients with hepatic metastasis from colorectal cancer. Hepatectomy is currently associated with a perioperative mortality rate of <5% and morbidity rate of 15% to 35% and achieves a 5-year survival rate of 20% to 46% [1–7, 14, 23–26]. In the present series, we found a mortality rate of 0%, a morbidity rate of 23%, and a 5-year survival rate of 58%, which are generally in agreement with the reported data.

In this series, 45% of patients undergoing curative resection of CRLM developed recurrence within 2 years of surgery. Early recurrence of liver metastases is the leading cause of death during the initial 5-year period after curative resection. In the present study, 4 out of 65 patients (6%) in the 2-year disease-free group and 29 out of 54 patients (54%) in the early recurrence group died during the initial 5-year period after resection. Death was attributable to metastatic colorectal cancer in all 29 patients with early recurrence who died within 5 years after resection. Chok et al. also reported that the presence of postoperative complications is the leading cause of death during the early period after curative resection of hepatocellular carcinoma [27]. Early recurrence occurred in approximately 74% of patients with postoperative morbidity, and postoperative morbidity was the only factor shown to be significantly associated with recurrence by multivariate analysis. Although several other preoperative and intraoperative factors also appeared to be associated with early

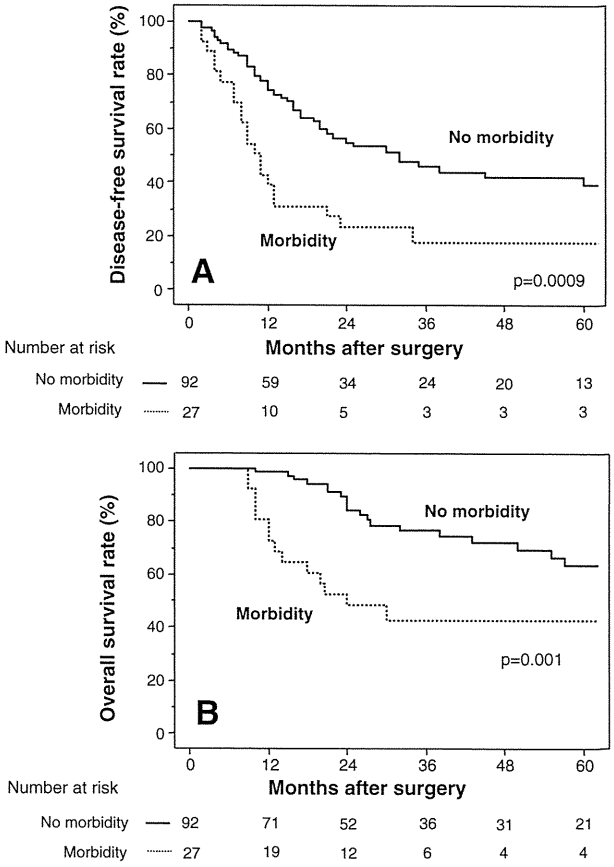

Fig. 1 Influence of postoperative morbidity on survival. Comparison of recurrence-free survival (**a**) and overall survival (**b**) after resection of liver metastases between patients with postoperative morbidity (*dotted lines*) and patients without morbidity (*unbroken lines*). The disease-free and overall survival rates of the two groups were significantly different (p=0.0009 and p=0.001, respectively). The number of patients at risk is shown below each graph

recurrence, our sample size was too small to confirm significance. Previously reported risk factors for early recurrence include tumor doubling time, CEA level, tumor size, multiple metastases, positive surgical margin, lymph node involvement, histology of the primary tumor, and clinical risk score [1, 8, 10, 14–19]. However, various studies have yielded conflicting results concerning the predictors of recurrence, and there is still debate about which factors are important. In the present series, the presence or absence of postoperative morbidity was found to be useful for predicting recurrence.

Postoperative morbidity after liver resection increases both the length of hospital stay and medical costs [28]. The impact of postoperative morbidity on the long-term outcome after cancer surgery has recently been investigated. A study analyzing data from the National Surgical Quality Improvement Program demonstrated that postoperative morbidity was associated with worse long-term survival after selected major operations [29], and a negative impact of postoperative morbidity on long-term outcome has also been documented after surgery for head and neck cancer [30], colorectal cancer [31, 32], esophageal cancer [33], and CRLM [34–37]. The precise mechanism by which postoperative morbidity influences the long-term outcome of cancer remains to be elucidated. Major surgery causes a systemic inflammatory response and immunosuppression [38], and it is possible that postoperative morbidity exacerbates this inflammatory response and/or immunosuppression. There has been speculation that prolonged systemic inflammation and immunosuppression associated with postoperative morbidity may promote the survival and subsequent growth of tumor micrometastases. The occurrence of infection, anastomotic leakage, and organ failure may, therefore, contribute to the survival of tumor cells after surgical resection [39–41]. In the present series, 10 out of 20 patients (50%) with postoperative morbidity in the early recurrence group had infection and 5 out of 20 patients (25%) had liver failure (Table 2). There have been four previous reports investigating the interactions between postoperative morbidity, postoperative recurrence of CRLM, and survival [34–37].

Nordlinger et al. [42] recently undertook a prospective randomized controlled trial of perioperative chemotherapy versus surgery alone for resectable CRLM and found increased postoperative morbidity together with better disease-free survival in the group receiving chemotherapy. However, the present study did not find any differences in the neoadjuvant or postoperative chemotherapy provided between the early recurrence and 2-year recurrence-free groups or between patients with and without postoperative morbidity (Tables 2 and 4). It is worth considering that postoperative morbidity presumably delays postoperative chemotherapy.

In Table 4, the lack of statistical differences between groups does not indicate equivalence. Patients with postoperative morbidity were more likely to have a clinical risk score >2 (52% vs. 33%), a positive surgical margin (30% vs. 15%), CEA >6 ng/ml (56% vs. 40%), and tumor size >3.5 cm (59% vs. 47%) than patients without morbidity, suggesting that the tumor burden was heavier in the high-morbidity group. The present study only evaluated a small group of patients, was retrospective in nature, and collected data from a long period of time.

Conclusion

Early recurrence is the leading cause of death during the initial 5-year period after curative resection of CRLM, and postoperative morbidity is a significant risk factor for early recurrence after curative resection. Efforts to further refine surgical techniques and perioperative management may, therefore, help to improve the long-term outcome of patients with metastatic colorectal cancer.

Conflicts of interest None.

References

1. Choti MA, Sitzmann IV, Iiburi MF et al (2002) Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 235:759–766
2. Rees M, Plant G, Bygrave S (1997) Late results justify resection for multiple hepatic metastases from colorectal cancer. Br J Surg 84:1136–1140
3. Sugihara K, Hojo K, Moriya Y et al (1993) Pattern of recurrence after hepatic resection for colorectal metastases. Br J Surg 80:1032–1035
4. Ohlsson B, Stenram U, Iranberg KG et al (1998) Resection of colorectal liver metastases: 25-year experience. World J Surg 22:268–276
5. Scheele I, Stangl R, Altendorf-Hofmann A et al (1991) Indication of prognosis after hepatic resection for colorectal secondaries. Surgery 110:13–29
6. Abdalla EK, Vauthey JN, Ellis LM et al (2004) Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 239:818–825
7. Pawlik TM, Scoggins CR, Zorzi D et al (2005) Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg 241:715–722
8. Nordlinger B, Guiguet M, Vaillant JC et al (1996) Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. Cancer 77:1254–1262
9. Fong Y, Cohen AM, Fortner JG et al (1997) Liver resection for colorectal metastases. J Clin Oncol 15:938–946
10. Fong Y, Fortner J, Sun RL et al (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 230:309–318
11. Kurtz JM, Amalric R, Brandone H et al (1989) Local recurrence after breast-conserving surgery and radiotherapy. Frequency, time course, and prognosis. Cancer 63:1912–1917
12. Minagawa M, Makuuchi M, Takayama T et al (2003) Selection criteria for repeat hepatectomy in patients with recurrent hepatocellular carcinoma. Ann Surg 238:703–710
13. Schrodter S, Hakenberg OW, Manseck A et al (2002) Outcome of surgical treatment of isolated local recurrence after radical nephrectomy for renal cell carcinoma. J Urol 167:1630–1633
14. Minagawa M, Makuuchi M, Torzilli G et al (2000) Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. Ann Surg 231:487–499
15. Adam R, Pascal G, Azoulay D et al (2003) Liver resection for colorectal metastases: the third hepatectomy. Ann Surg 238:871–883
16. Ueno H, Mochizuki H, Hatsuse K et al (2000) Indications for treatment strategies of colorectal liver metastases. Ann Surg 231:59–66
17. Lise M, Bacchetti S, Da Pian P et al (2001) Patterns of recurrence after resection of colorectal liver metastases: prediction by models of outcome analysis. World J Surg 25:638–644
18. Schindl M, Wigmore SJ, Currie EJ et al (2005) Prognostic scoring in colorectal cancer liver metastases. Arch Surg 140:183–189
19. Mutsaerts EI, van Ruth S, Zoetmulder FA et al (2005) Prognostic factors and evaluation of surgical management of hepatic metastases from colorectal origin: a 10-year single-institute experience. J Gastrointest Surg 9:178–186
20. Strasberg SM, Belghiti J, Clavn P-A et al (2000) The Brisbane 2000 terminology of liver anatomy and resection. Terminology Committee of the International Hepato-Pancreato-Biliary Association. HPB 2:333–339
21. Couinaud C (1957) Les hepatectomies elargies. In: Couinaud C (ed) Le Foie: Etudes Anatomiques et Chirurgicales. Masson, Paris, pp 400–409
22. Clavien PA, Barkun J, de Oliveira ML et al (2009) The Clavien–Dindo classification of surgical complications—five-year experience. Ann Surg 250:187–196
23. Scheele J, Stangl R, Altendorf-Hofmann A et al (1995) Resection of colorectal liver metastases. World J Surg 19:59–71
24. Ambiru S, Miyazaki M, Isono T et al (1999) Hepatic resection for colorectal metastases: analysis of prognostic factors. Dis Colon Rectum 42:632–639
25. Harms J, Obst T, Thorban S et al (1999) The role of surgery in the treatment of liver metastases for colorectal cancer patients. Hepatogastroenterology 46:2321–2328
26. Figueras J, Valls C, Rafecas A et al (2001) Resection rate and effect of postoperative chemotherapy on survival after surgery for colorectal liver metastases. Br J Surg 88:980–985
27. Chok KS, Ng KK, Poon RT et al (2009) Impact of postoperative complications on long-term outcome of curative resection for hepatocellular carcinoma. Br J Surg 96:81–87
28. Dimick JB, Pronovost PJ, Cowan JA et al (2003) Complications and costs after high-risk surgery: where should we focus quality improvement initiatives? J Am Coll Surg 196:671–678
29. Khuri SF, Henderson WG, DePalma RG et al (2005) Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg 242:326–341, discussion 341–343
30. de Melo GM, Ribeiro KC, Kowalski LP et al (2001) Risk factors for postoperative complications in oral cancer and their prognostic implications. Arch Otolaryngol Head Neck Surg 127:828–833
31. McArdle CS, McMillan DC, Hole DJ et al (2005) Impact of anastomotic leakage on long-term survival of patients undergoing curative resection for colorectal cancer. Br J Surg 92:1150–1154
32. Law WL, Choi HK, Lee YM et al (2007) The impact of postoperative complications on long-term outcomes following curative resection for colorectal cancer. Ann Surg Oncol 14:2559–2566
33. Rizk NP, Bach PB, Schrag D et al (2004) The impact of complications on outcomes after resection for esophageal and gastroesophageal junction carcinoma. J Am Coll Surg 198:42–50
34. Vigano L, Ferrero A, Tesoriere RL et al (2008) Liver surgery for colorectal metastases: results after 10 years of follow-up. Long-term survivors, late recurrences, and prognostic role of morbidity. Ann Surg Oncol 15:2458–2464
35. Ito H, Chandrakanth A, Gonen M et al (2008) Effect of postoperative morbidity on long-term survival after hepatic resection for metastatic colorectal cancer. Ann Surg 247:994–1002
36. Farid SG, Aldouri A, Morris-Stiff G et al (2010) Correlation between postoperative infective complications and long-term outcomes after hepatic resection for colorectal liver metastasis. Ann Surg 251:91–100
37. Laurent C, Cunha AS, Couderc P et al (2003) Influence of postoperative morbidity on long-term survival following liver resection for colorectal metastases. Br J Surg 90:1131–1136
38. Lundy J, Ford CM (1983) Surgery, trauma and immune suppression. Evolving the mechanism. Ann Surg 197:434–438
39. Hirai T, Yamashita Y, Mukaida H et al (1998) Poor prognosis in esophageal cancer patients with postoperative complications. Surg Today 28:576–579

40. Petersen S, Freitag M, Hellmich G et al (1998) Anastomotic leakage: impact on local recurrence and survival in surgery of colorectal cancer. Int J Colorectal Dis 13:160–163
41. Mynster T, Christensen IJ, Moesgaard F et al (2000) Effects of the combination of blood transfusion and postoperative infectious complications on prognosis after surgery for colorectal cancer. Danish RANXOS Colorectal Cancer Study Group. Br J Surg 87:1553–1562
42. Nordlinger B, Sorbye H, Glimelius B et al (2008) Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 371:1007–1016

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ORIGINAL ARTICLE

A Prospective Randomized Controlled Trial of Preoperative Whole-Liver Chemolipiodolization for Hepatocellular Carcinoma

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Abstract
Background We previously reported that preoperative chemolipiodolization of the whole liver is effective for reducing the incidence of postoperative recurrence and prolonging survival in patients with resectable hepatocellular carcinoma (HCC). The present randomized controlled trial was performed to evaluate the influence of preoperative transcatheter arterial chemoembolization (TACE) on survival after the resection of HCC.
Methods Operative results and long-term outcome were prospectively compared among 42 patients who received only selective TACE targeting the tumor (selective group), 39 patients who received TACE targeting the tumor plus chemolipiodolization of the whole liver (whole-liver group), and 43 patients without preoperative TACE or chemolipiodolization (control group).
Results There were no serious side effects of TACE or chemolipiodolization and the operative outcomes did not differ among the three groups. Even though preoperative TACE induced complete tumor necrosis, there were no significant differences in the pattern of intrahepatic recurrence or the time until recurrence among the three groups. There were also no significant differences in disease-free survival or overall survival among the three groups, even among patients with larger tumor size.
Conclusion These results indicate that preoperative selective TACE and whole-liver chemolipiodolization plus TACE do not reduce the incidence of postoperative recurrence or prolong survival in patients with resectable HCC.

Keywords Hepatocellular carcinoma · Preoperative chemolipiodolization · Whole liver · Hepatectomy · Randomized controlled trial

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide [1]. Although the majority of patients are still found in Asia and Africa, recent studies have shown that the incidence and mortality rate of HCC are rising in North America and Europe [2, 3]. There has been an increase in reports of non-surgical therapeutic options for small HCC, such as percutaneous ethanol injection therapy [4], microwave coagulation therapy [5], and percutaneous radiofrequency ablation (RFA) [6], but there is ongoing controversy regarding the best method of treating small tumors. In Japan, liver transplantation is not a practical option for most HCC patients, because the national health insurance scheme only covers transplantation for patients with decompensated cirrhosis whose tumors fit the Milan criteria. Resection is, therefore, generally the first-line treatment for patients with small tumors and underlying chronic liver disease, but the long-term survival rate after

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potentially curative resection of HCC is still unsatisfactory because of the high rate of recurrence [7]. To improve prognosis, it is important to prevent the recurrence of HCC after its initial resection, but standard therapy for intrahepatic metastasis has not yet been developed.

With various improvements in interventional radiology, transcatheter arterial chemoembolization (TACE) has become an increasingly important palliative treatment for HCC. Initially, TACE was only performed for unresectable HCC, as well as for some early tumors that were extremely difficult to resect. More recently, TACE has been used as preoperative adjuvant therapy in patients who have resectable HCC with the hope that it may improve survival [8–13]. Based on the current evidence, however, preoperative TACE is not routinely recommended for patients undergoing hepatectomy to treat resectable HCC [14–16], and TACE may be contraindicated in patients with cirrhosis because it can lead to the progressive deterioration of liver function [14]. Whether preoperative TACE can improve the long-term survival of HCC patients is still unclear, and there have been only three randomized controlled trials evaluating the influence of preoperative TACE on survival [15, 17, 18]. We previously reported that preoperative chemolipiodolization of the entire liver is effective for reducing the incidence of postoperative recurrence and for prolonging survival in patients with resectable HCC [19]. Accordingly, the present randomized controlled trial was conducted to better assess the influence of preoperative TACE combined with whole-liver chemolipiodolization on survival after the resection of HCC.

Patients and Methods

Patients

Between January 2004 and June 2007, 124 patients with HCC underwent curative hepatic resection at our institution. A curative operation was defined as the resection of all detectable tumors. The eligibility criteria for inclusion in this study were as follows: (1) age 20–80 years; (2) a preoperative diagnosis of HCC with no previous treatment; (3) no other malignancies; (4) Child–Pugh score A or B; (5) leukocyte count $\geq$3,000/mm^3; (6) hemoglobin level $\geq$9.5 g/dl; (7) platelet count $\geq$50,000/mm^3; (8) serum creatinine level <1.2 mg/dl; (9) total bilirubin <2.0 mg/dl; (10) local nodular disease without extrahepatic metastasis; and (11) Eastern Cooperative Oncology Group (ECOG) performance status 0–1 [20]. The etiology of HCC (HCV-related or other [HBV-related or non-B, non-C-related]) and the size of the tumor on imaging were taken into consideration when dividing patients into the three groups. The sample size was estimated based on our previously reported 3-year disease-free survival rates in selective and whole-liver groups, being 25 and 60%, respectively [19]. We needed 37 patients in each group for a type I error rate of 5% and a type II error rate of 20% with a two-tailed test. Among the 124 patients, TACE was performed preoperatively in 81. Patients were randomized to receive chemolipiodolization with gelatin sponge (equal to TACE) targeting the tumor (selective group, $n = 42$), chemolipiodolization with gelatin sponge (equal to TACE) targeting the tumor plus chemolipiodolization without gelatin sponge for the non-cancerous liver (whole-liver group, $n = 39$), or no preoperative TACE (control group, $n = 43$). The study protocol was explained to all patients, and they understood that they would be randomly selected for one of the above three groups. All patients gave written informed consent to participation in the trial. They were randomized by the envelope method and were informed of the result of the randomization before angiography. All operations were performed by the same surgeon, who had experience of over 700 hepatic resections. The protocol for this study was approved by the ethics committee of Kansai Medical University. The primary outcome measures were disease-free survival rate and overall survival rate. Secondary outcome measures included procedure-related complications and hospital mortality (Fig. 1).

Chemolipiodolization

A catheter was selectively inserted into the right or left hepatic artery, a segmental artery, or a subsegmental artery by Seldinger's method. In the selective group, TACE was performed via the right hepatic artery in 16 patients, the left hepatic artery in 10 patients, a segmental artery in 9 patients, and a subsegmental artery in 7 patients. In the whole-liver group, TACE (i.e., chemolipiodolization with gelatin sponge) was performed via the right hepatic artery in 18 patients and the left hepatic artery in 13 patients to target the tumor, while chemolipiodolization alone was performed on the non-cancerous side via the left or right hepatic artery. In a further 8 patients, TACE was performed via a right or left subsegmental artery to target the tumor and chemolipiodolization of the non-cancerous liver was performed via the right and left hepatic arteries as the catheter was withdrawn. The selective group was treated with epirubicin (Farmorubicin) at a mean ($\pm$ standard deviation [SD]) dose of 47.0 $\pm$ 17.8 mg, iodized oil (Lipiodol) at a mean volume of 3.8 $\pm$ 2.1 ml, and gelatin sponge particles. In the whole-liver group, epirubicin (28.1 $\pm$ 5.5 mg), Lipiodol (2.9 $\pm$ 1.4 ml), and gelatin sponge particles were used to treat the tumor, while only epirubicin (22.2 $\pm$ 6.2 mg) and Lipiodol (1.9 $\pm$ 0.8 ml) were infused into the non-cancerous liver. In the control group, only angiography was performed.